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09/824,924	04/03/2001	Christopher B. Eckman	07039-235001	2130

7590

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EXAMINER

CHERNYSHEV, OLGA N

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 07/15/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/824,924

Applicant(s)

ECKMAN ET AL.

Examiner

Olga N. Chernyshev

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 7-9, 11-15 and 40-48 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 7-9, 11-15 and 40-48 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7. 6) ☐ Other:

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## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election without traverse of Group II in Paper No. 10 is acknowledged. Claims 1-6, 10 and 16-39 have been cancelled, claim 7 has been amended and claims 40-48 have been added as requested in amendment of Paper No.11. Claims 7-9, 11-15 and 40-48 are pending in the instant application.

Claims 7-9, 11-15 and 40-48 are under examination in the instant office action.

### ***Sequence compliance***

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825. Specifically, no sequence listing has been provided which includes the amino acid sequence presented page 12, third paragraph of the instant specification. Applicant needs to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO: ) be made in the specification and claims wherever a

reference is made to that sequence. For rules interpretation Applicant may call (703) 308-1123.  
See M.P.E.P. 2422.04.

### *Specification*

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see page 12, third paragraph and page 13, first paragraph, for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The use of the trademarks has been noted in this application, page 23, first paragraph and page 25, first paragraph, for example. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is advised to check the text of the specification for other possible hyperlinks and trademarks.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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4. Claims 7-9, 11-15 and 40-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods as encompassed by the claims involving ECE-1a and ECE-1b, does not reasonably provide enablement for such method involving any ECE polypeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant invention (claims 7-9, 11-15 and 40-48) is directed to a method of identifying a compound that increases the A $\beta$ -cleaving activity of an ECE polypeptide and to a method of identifying a compound that has anti-hypertension activity but does not cause an increase in the level of A $\beta$ , which involves ECE polypeptide. As it is stated by Applicant "[t]he invention identifies endothelin-converting enzymes (ECE) as A $\beta$  degrading enzymes" (page 1, fourth paragraph of the instant specification) The specification provides description of *in vitro* assays using ECE-1a and ECE-1b polypeptides and explanation how the *in vitro* assays of the working examples can be extrapolated for *in vivo* methods. However, the instant specification is not found to be enabled for the full scope of claimed methods, which involves the use of any ECE polypeptide for the following reasons. The instant specification does not provide meaningful information on how to use the claimed method employing other forms of ECE as A $\beta$  degrading enzymes except for ECE-1a and ECE-1b, thus, requiring undue experimentation on part of one skilled in the art to discover how to practice the claimed invention.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature

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of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

The state of the prior art is such that there is no indication that all of the proteins encompassed by the term "ECE", class of enzyme that catalyzes the final step in the biosynthesis of the vasoconstrictor endothelins, would be involved in processing of amyloid-beta, A $\beta$  peptide. According to the instant specification, "ECEs (3.4.24.71) are a class of structurally- and functionally-related type II integral membrane zinc metalloproteases named for their ability to hydrolyze a family of biologically inactive intermediates, big ETs, exclusively at Trp/Val-Ile bond at amino acid residues 21-22 to form the potent vasoconstrictors, ET" (page 6, third paragraph of the instant specification). It is further stated that "ECE-1 and ECE-2 preferentially hydrolyze big ET-1 [and] ECE-3 [...] is highly specific for the conversion of big ET-3" (page 7, first paragraph). Because there is no indication in the prior art that all ECEs would cleave A $\beta$ , one skilled in the art would not have a reasonable expectation that other isoforms of ECE polypeptides will cleave A $\beta$ . Because the instant specification fails to provide neither such guidance nor working examples of a method, which employs an ECE other than ECE-1a or ECE-1b, a skilled artisan would have to resort to undue experimentation to practice the full scope of the claimed invention.

The standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use with a reasonable expectation of success. Considering that substrate specificity is a major issue in proteolytic activity of enzymes, and some structurally related proteases can exhibit different activity toward the same, for example,

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biologically active peptides, like ECE-1 and neprilysin (Johnson et al., J.Biol.Chem., Vol.274, 7, pp.4-53-58, see the abstract), one of ordinary skill in the art would readily recognize the unpredictability of using different isoforms of ECE for possible cleavage of A $\beta$ . The publication of Johnson et al. further discloses specific patterns of cleavage by soluble ECE-1 (see p."7 of 13" of the reference copy, second paragraph), none of which includes amino acid bonds in the structure of A $\beta$ . A skilled artisan would not know how to use the claimed method when it involves other forms of ECE because there is no indication provided in the instant specification, that other forms of ECE would possess the same critical activity as ECE-1a and ECE-1b. The instant specification fails to provide any evidence or sound scientific reasoning that would support a conclusion that any ECE isoform would be as specific and effective in cleavage of A $\beta$  as the disclosed ECE-1a and ECE-1b.

Thus, in view of the lack of teachings and unpredictability of the art set forth earlier, and also the total absence of the working examples, the instant specification is not found to be enabling for the full scope of methods as encompassed by the claims 7-9, 11-15 and 40-48 involving any ECE polypeptides. It would require undue experimentation and making a substantial inventive contribution for the skilled artisan to discover how to practice the full scope of Applicant's invention as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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5. Claims 7-9, 40-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
6. Claim 7 is vague and indefinite because the term "ECE" can have different meanings unless it is described in full before the first occurrence of the acronym.
7. Claims 8-9 and 40-41 are indefinite for being dependent from indefinite claim.

### *Conclusion*

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 782-9306 for regular communications and (703) 782-9307 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original



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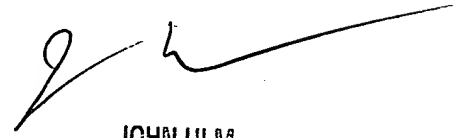
signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D.  
July 12, 2002

*OC*



JOHN ULM  
PRIMARY EXAMINER  
GROUP 1800